

Bringing Technology to Day-to-Day Asthma Management

Integrated information technology, big data, and predictive analytics have recently transformed a myriad of industries. These innovations promise to disrupt and revolutionize the practice of medicine.

However, since the transition from paper to electronic health records began three decades ago, the translation of clinical data into evidence-based practice has been slower than predicted. Systematic barriers, such as multiple electronic medical records, complex secondary data that are difficult to manage and test for accuracy, ontological challenges, such as subjectivity and variation in disease presentation, multiple data collection devices, U.S. Food and Drug Administration approval for devices and software, and important privacy and Health Insurance Portability and Accountability Act concerns, all hinder the ease with which we can integrate these technologies into our practice of medicine.

Patients with pediatric asthma, one of the most common chronic diseases of childhood, represent an obvious and potentially high-value target population for which big data and machine learning-based analytic tools can improve care and decrease costs. Electronic health innovation may allow for personalized treatment and monitoring, integrating vast amounts of data, including patient clinical characteristics, physiologic data, environmental exposure, medication selection and dosing, lung function, and even genomics (1).

Currently, asthma management is focused on gaining optimal asthma control via understanding of the impairment and risk domain, specifically, exacerbation risk and disease progression balanced with medication adverse effects. There is developing information on identifying patients at risk for asthma exacerbations (2), including a strong influence of prior exacerbation frequency and seasonal trends. However, our information is limited on identifying features of an emerging exacerbation that would allow for pre-emptive interventions. Current objective markers, such as peak flow monitoring, tend to lead to many false positives in exacerbations (3).

In this issue of the *Journal*, the proof-of-concept study by Huffaker and colleagues (pp. 320–328) seeks to associate nocturnal physiologic data (collected via commercial contactless bed sensor) with self-reported asthma symptoms (4). This report contributes to the area of asthma assessment and noninvasive home monitoring. The investigators used machine learning to identify effort-independent physiologic patterns and characteristics to objectively predict pediatric asthma control deterioration. The study included 16 primarily male participants aged 5–18 years with persistent asthma; asthma symptoms were collected every 2 weeks via parental self-reporting using the asthma control test and medication reporting; 10 of those patients experienced

asthma symptoms. Analysis and algorithm training used nocturnal physiologic data during symptomatic time periods only, excluding periods immediately before and after the time of patient-reported symptom worsening. Testing of the algorithm's predictive sensitivity and specificity was performed on data collected 14 days before perceived symptom onset. Subgroup analysis was also completed on two subjects. To summarize, a random forest model was used to generate an algorithm that detected asthma symptoms with 47% sensitivity, 96% specificity, and 87% accuracy, with mean heart rate as the principal parameter driving the prediction. In addition, the model predicted asthmatic symptoms 35% of the time on the day before onset of perceived symptoms. The results of the subgroup analysis on two patients suggest that sensitivity may be altered by subject characteristics; however, larger sample sizes would be needed to confirm.

The device outputs heavily leveraged measured heart rate, using a technique called ballistocardiography to calculate other parameters, including respiratory rate, vital sign variability, cardiac stroke volume, and $\dot{V}O_2$. A substantial proportion of data and subjects (>50% in this study) were excluded due to missing data and outcomes.

Application of deep learning to physiologic data has been used to identify patterns useful in predicting cardiorespiratory deterioration and sentinel events, such as sepsis and hypovolemic shock (5, 6). Similarly, patient questionnaires to assess asthma control in the clinical setting have been well validated, such as the specific questionnaire used in this study: the Asthma Control Test (7). Predicting pediatric asthma exacerbations/clinical deterioration combining health care data and physiologic lung function measures has focused on the creation of models for clinical prediction based on accumulated patient characteristics, including genetics and biomarkers, logistic regression, and machine learning techniques (8, 9). As there have not yet been randomized, controlled trials rigorously validating any of these models, the gold standard for identifying a highly specific and sensitive indicator for the onset of an asthma exacerbation is unknown. A study by Luo and colleagues in 2015 (10) combined environmental information (including pollen and mold counts and viral activity) with patient/parent-collected symptom data and demographic data from 210 children. Through the use of machine learning, this model was able to predict asthma control deterioration 1 week ahead with an accuracy of 71.8%, a sensitivity of 73.8%, and a specificity of 71.4%. Both this study and the work by Huffaker and colleagues suggest that model sensitivity increases with increased asthma symptoms, suggesting that these prediction models may be most useful in patients with exacerbation-prone asthma (4, 10).

Prediction models that leverage machine learning to monitor asthma control have common limitations; asthma is a fundamentally heterogeneous disease with many phenotypes (11), and identification of ground truth with which to train the algorithm is a challenge. In both these studies, ground truth for prediction was based in large part on patient recall and perception. Challenges with patient medication adherence, poor symptom perception, and delays in seeking care are common to many chronic illnesses, including

A.I.M. has received research support from the NIH and the NHLBI; R.R.D. has received research support from QUALCOMM and the Schramm Foundation; and S.J.S. has received research support from the NIH, the NHLBI, GlaxoSmithKline, and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program.

Originally Published in Press as DOI: 10.1164/rccm.201805-0845ED on May 30, 2018

asthma. Although a tool that can monitor and alert patients and clinicians to symptoms early has value, adherence and sustainable use of mobile monitoring technology (fitness trackers, phone applications, and medication monitors), particularly those that require patient effort, continue to be challenging (12, 13). To address this, the work by Huffaker and colleagues endeavors to use passively collected objective data. Another common hurdle encountered by this study and home monitoring technologies are the logistical device limitations (accuracy, U.S. Food and Drug Administration approval, disconnection, timely upload/download, device malfunctions, accidental repositioning, etc.), which leads to a substantial amount of missing data and artifact that weakens study power (13–15).

Huffaker and colleagues should be commended for their foundational work presented in this report. To run the last mile of the clinical translation marathon, prediction work like this must be tied to relevant and measurable clinical outcomes (16), integrated into clinical and system work flow, and be easily interpreted and adopted by providers and staff. For pediatric asthma, important outcomes include exacerbation rate, severity, longitudinal asthma control, medication burden, and patient quality of life. Thoughtful collaboration between healthcare systems, healthcare payers, private sector companies, data scientists, clinicians, and their patients is essential to designing and implementing technologic tools that can accurately decode the challenges in assessing the variability of disease presentation and enable personalized solutions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Amanda I. Messinger, M.D.
Robin R. Deterding, M.D.
Stanley J. Szeffler, M.D.
Department of Pediatrics
University of Colorado School of Medicine and Children's Hospital Colorado
Aurora, Colorado

ORCID ID: 0000-0002-6911-3199 (S.J.S.).

References

1. Szeffler SJ. Asthma across the lifespan: time for a paradigm shift. *J Allergy Clin Immunol* [online ahead of print] 5 Apr 2015; DOI: 10.1016/j.jaci.2018.03.010.
2. Hoch HE, Calatroni A, West JB, Liu AH, Gergen PJ, Gruchalla RS, et al. Can we predict fall asthma exacerbations? Validation of the seasonal asthma exacerbation index. *J Allergy Clin Immunol* 2017;140:1130–1137.e5.
3. Covar RA, Szeffler SJ, Zeiger RS, Sorkness CA, Moss M, Mauger DT, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol* 2008;122:741–747.e4.
4. Huffaker MF, Carchia M, Harris BU, Kethman WC, Murphy TE, Sakarovich CCD, et al. Passive nocturnal physiologic monitoring enables early detection of exacerbations in children with asthma: a proof-of-concept study. *Am J Respir Crit Care Med* 2018;198:320–328.
5. Fairchild KD, Lake DE, Kattwinkel J, Moorman JR, Bateman DA, Grieve PG, et al. Vital signs and their cross-correlation in sepsis and NEC: a study of 1,065 very-low-birth-weight infants in two NICUs. *Pediatr Res* 2017;81:315–321.
6. Moulton SL, Mulligan J, Santoro MA, Bui K, Grudic GZ, MacLeod D. Validation of a noninvasive monitor to continuously trend individual responses to hypovolemia. *J Trauma Acute Care Surg* 2017;83(1 Suppl):S104–S111.
7. Cloutier MM, Schatz M, Castro M, Clark N, Kelly HW, Mangione-Smith R, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immunol* 2012;129(3 Suppl):S24–S33.
8. Luo G, Nkoy FL, Stone BL, Schmick D, Johnson MD. A systematic review of predictive models for asthma development in children. *BMC Med Inform Decis Mak* 2015;15:99.
9. Das LT, Abramson EL, Stone AE, Kondrich JE, Kern LM, Grinspan ZM. Predicting frequent emergency department visits among children with asthma using EHR data. *Pediatr Pulmonol* 2017;52:880–890.
10. Luo G, Stone BL, Fassl B, Maloney CG, Gesteland PH, Yerram SR, et al. Predicting asthma control deterioration in children. *BMC Med Inform Decis Mak* 2015;15:84.
11. Pijnenburg MW, Szeffler S. Personalized medicine in children with asthma. *Paediatr Respir Rev* 2015;16:101–107.
12. Hoch H, Kempe A, Brinton J, Szeffler S. Feasibility of medication monitoring sensors in high risk asthmatic children. *J Asthma* [online ahead of print] 11 Apr 2018; DOI: 10.1080/02770903.2018.1446979.
13. Chan AH, Reddel HK, Apter A, Eakin M, Riekert K, Foster JM. Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma. *J Allergy Clin Immunol Pract* 2013;1:446–454.
14. Lechtzin N, Mayer-Hamblett N, West NE, Allgood S, Wilhelm E, Khan U, et al.; eICE Study Team. Home monitoring of patients with cystic fibrosis to identify and treat acute pulmonary exacerbations: eICE Study results. *Am J Respir Crit Care Med* 2017;196:1144–1151.
15. Reddel HK, Ware SI, Salome CM, Jenkins CR, Woolcock AJ. Pitfalls in processing home electronic spirometric data in asthma. *Eur Respir J* 1998;12:853–858.
16. Cabitza F, Rasoini R, Gensini GF. Unintended consequences of machine learning in medicine. *JAMA* 2017;318:517–518.

Copyright © 2018 by the American Thoracic Society

To Withdraw or Not to Withdraw Inhaled Corticosteroids from Triple Therapy in Chronic Obstructive Pulmonary Disease

The role of inhaled corticosteroid treatment for chronic obstructive pulmonary disease (COPD) has long been debated. Monotherapy

with inhaled corticosteroids (ICS) has shown relatively little benefit in patients with COPD aside from a reduction in the risk of exacerbations, particularly in patients with more severe airflow obstruction (1), and is not currently recommended. However, fixed-dose combinations of ICS with a long-acting β -agonist (LABA) have consistently shown greater efficacy for reducing

Originally Published in Press as DOI: 10.1164/rccm.201805-0979ED on June 19, 2018